BIOGRAPHICAL SKETCH

NAME: Khurana, Vikram MD PhD

eRA COMMONS USER NAME (credential, e.g., agency login): VKHURANA

POSITION TITLE: Chief, Division of Movement Disorders; Tracy T. Batchelor Endowed Chair in Neurology, Brigham & Women's Hospital and Harvard Medical School; Principal Investigator, Ann Romney Center for Neurologic Diseases; Principal Faculty, Harvard Stem Cell Institute; Associate Member, Broad Institute of Harvard and MIT.

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Sydney	B.A.	05/00	Applied Mathematics
University of Sydney	M.B., B.S	05/00	**Medicine/Surgery** (M.D.)
Harvard University	Ph.D.	06/06	**Neurobiology** (Advisor: Mel Feany, Ph.D.)
Brigham and Women's Hospital		06/07	**Medical Internship**
Brigham and Women's Hospital / Massachusetts General Hospital		06/10	**Neurology Residency**
Massachusetts General Hospital		05/12	**Neurology Fellowship** (Movement Disorders / Ataxia)
Whitehead Institute of Biomedical Research Massachusetts Institute of Technology		06/15	**Postdoctoral Fellowship** (Advisors: Susan Lindquist, Ph.D.; Rudolf Jaenisch, Ph.D.)

A. Personal Statement

As a clinician scientist, my overarching goal is to understand the heterogeneity of patients with neurodegenerative diseases, and to find targeted interventions that prevent or modify disease progression in these patients. The unifying thread in my scientific work has been the development and application of tractable and unbiased genetic tools to dissect protein-misfolding events that lie at the core of neurodegeneration and to do so in specific cell-types of the nervous system. My work has led to identification of important mechanisms of tau and alpha synuclein-mediated neurotoxicity. For example, I co-developed a yeast-to-human neuron platform capable of harnessing high-throughput genetic and small-molecule approaches in yeast to identify and reverse core mechanisms of neurodegeneration in patient stem cell-derived neurons. This work enabled drug discovery and target identification for neurodegeneration through unbiased phenotypic screens and has led already to one potential class of drugs for Parkinson's disease (stearoyl-coA desaturase inhibitors) entering clinical trial.

Over the years, we have combined genetic interaction and proximity label mapping of alpha- synucleinopathy with computational approaches to provide the first molecular interaction network of alpha-synucleinopathy. These molecular networks uncovered highly specific biological connections between protein-misfolding and the genetic risk factors that predispose to these diseases and are candidate penetrance factors. They also uncovered a novel direct links between alpha-synuclein and mRNA biding and cytoskeletal proteins. We are now using our networks to probe questions in functional genomics and gene-environment interactions in Parkinson's disease and have established novel glioneuronal iPSC-based models to do so. Our work is truly bench-to-bedside and back to bench. For example, we recently in our MyTrial program completed the first known parallel trial "in the dish" in human stem cell models and in matched patients.

I enjoy bringing diverse ideas and disciplines to bear on important problems. My work has always been multi-faceted and deeply collaborative with other investigators across disciplines, from math to chemistry and biology. Beyond diversity in science, I am committed to mentoring women and minorities. In laboratory, currently six individuals identify as minority and our lab is majority women. Lab members hold ten different citizenships and speak 14 languages. I am a past Fulbright scholar. In 2018, I was named a Robertson Investigator of the New York Stem Cell Foundation and a George C. Cotzias Fellow of the American Parkinson's Disease Association. In 2023 I received the Derek Denny-Brown Award of the American Neurologic Association. I am the inventor on five patent filings that have been licensed to biotech companies.

Key Citations / Patents:

1. **Khurana V***[o], Peng J*, Chung CY*, Auluck PK, Fanning S, Tardiff DF, Bartels T, Koeva M, Benyamini H, Lou Y, Nutter-Upham A, Tuncbag N, Baru V, Freyzon Y, Costanzo M, San-Luis B, Schöndorf DC, Barrasa MI, Caraveo G, Ehsani S, Sanjana N, Zhong Q, Gasser T, Vidal M, Deleidi M, Boone C, Fraenkel E[o], Berger B[o] and Lindquist S. Genome-scale molecular networks link diverse neurodegenerative disease genes to alpha-synuclein through specific molecular pathways. ***Cell Systems*** 2017 4:157–170.e14. PMCID: PMC5388136 *Co-first and [o]co-corresponding authors. *PATENT-1: Cellular discovery platform for neurodegenerative diseases; US11047848B2; published 02/2016; PATENT-2: "Methods for building genomic networks and uses thereof" Patent Application WIBR-162-001, filed 02/2017 and published 08/21.*
2. Hallacli E, Kayatekin C, Nazeen S , Wang X, Sheinkopf Z, Sathyakumar S, Sarkar S, Jiang X, Dong X, Di Maio R, Wang W, Keeney MT, Daniel Felsky, Sandoe J, Vahdatshoar A, Mani DR, Udeshi ND, Carr SA, de Jager P, Myers CL, Greenmyre TJ, Lindquist S, Bartel DP, Sunyaev S, Feany MB, Chung CY and **Khurana V**[*]. The Parkinson's disease protein alpha-synuclein is a modulator of Processing-bodies and mRNA stability. ***Cell***. 2022 Jun 9;185(12):2035-2056.e33. PMCID: PMC9394447. *PATENT-3: "Induced proteinopathy models" Patent Application BWH 25182 (FR Ref: 2618-0202P01), filed 11/18/2021.*
3. Lam I, Ndayisaba A, Lewis AJ, Fu YH, Zaccagnini L, Sandoe J, Sanz R, Vahdatshoar A, Martin TD, Nader M, Ichihashi T, Tripathi A, Ramalingam N, Oettgen C, Bartels T, Schäbinger M, Jiang X, Verma A, Yu X, Hyles K, Park C, Theunissen TW, Wang H, Jaenisch R, Stevens B, Stefanova N, Wenning G, Luk KC, Pernaute RS, Gómez-Esteban JC, Felsky D, Kiyota Y, Sahni N, Yi S, Chung CY, Stahlberg H, Abizanda IF, Schöneberg J, Elledge SJ, Dettmer U, Halliday GM, Bartels T, and **Khurana V**. Rapid iPSC inclusionopathy models shed light on formation, consequence and molecular subtype of proteinaceous a-synuclein inclusions. ***Neuron,*** https://doi.org/10.1016/j.neuron.2024.06.002 (July 29 2024). *PATENT-3: "Induced proteinopathy models" Patent Application BWH 25182 (FR Ref: 2618-0202P01), filed 11/18/2021. PATENT-4: ATN1 CAG expansion and ASO-based therapeutic development in dentatorubral-pallidoluysian atrophy. BCH:2023-217. PATENT-5: PROTEOLYSIS TARGETING CHIMERAS FOR TREATING NEURODEGENERATION" (filed: United States Patent and Trademark Office on July 18, 2023, as application 63/527,519).*

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2024-	Tracy T. Batchelor Endowed Chair in Neurology, MassGeneral Brigham.
2022-	Associate Professor of Neurology Harvard Medical School
2021	Faculty, PhD Program in Biological and Biomedical Sciences
2019-	Team Lead, Australian Parkinson Mission.
2019-	Honorary Fellow, Garvan Institute, Sydney, Australia.
2018-	Chief, Division of Movement Disorders, Brigham and Women's Hospital
2017-	Associate Member, Broad Institute of Harvard and MIT
2016-	Assistant Professor in Neurology, Harvard Medical School
2016-	Principal Faculty, Harvard Stem Cell Institute
2012-2015	Attending Neurologist (Assistant in Neurology). Massachusetts General Hospital, Boston, MA
2010-2015	Postdoctoral Fellow, Lindquist and Jaenisch Laboratories, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge MA
2010-2016	Instructor in Neurology, Harvard Medical School, Boston MA
2010-2012	Clinical and Research Fellow in Neurology (Ataxia / Movement Disorders). Massachusetts General Hospital, Boston, MA
2010-	Board Certification, American Board of Psychiatry and Neurology (ABPN)
2007-2010	Resident (Neurology), Partners Neurology, Massachusetts General and Brigham and Women's Hospitals, Harvard Medical School, Boston MA
2006-7	Intern (Internal Medicine), Brigham and Women's Hospital, Boston MA
2002-4	Resident Adviser, Graduate School of Arts and Sciences, Cambridge MA
2001-6	Graduate Student, Harvard University, Cambridge MA
2000	Intern (Medicine, Surgery), Prince of Wales Hospital, Sydney, Australia

Honors

2024-	Vikram Khurana Endowed Chair in Neurology at MassGeneral Brigham (currently to be known as the Tracy T. Batchelor Endowed Chair in Neurology) is endowed by the Simches family.
2023	Derek Denny-Brown Award, American Neurologic Association (highest annual award)
2019-2022	Dr. George Cotzias Memorial Fellowship of American Parkinson's Disease Association
2019-2024	Robertson Stem Cell Investigator of New York Stem Cell Foundation
2018-2020	Brigham Research Institute (BRI) Director's Transformative Award
2018	Bishop Dr. Karl Golser Prize for Research in Atypical Parkinsonian Disorders
2016	National Ataxia Foundation, Young Investigator Award
2015	Lasker Clinical Research Scholarship (Intramural NIH) – *Declined*
2014	Multiple System Atrophy Coalition Inaugural Seed Grant
2013-2014	Harvard Neurodiscovery Center Neurodegenerative Disease Pilot Study Grant
2011-2014	American Brain Foundation-Parkinson's Disease Foundation Clinician-Scientist Development Three-Year Award
2010	American Academy of Neurology Clinical Research Training Fellowship
2005	Harvard Medical School Albert J. Ryan Fellowship and Illick Fellow of the Ryan Foundation
2005	Harvard Medical School Albert J. Ryan Fellowship and Illick Fellow of the Ryan Foundation
2001	Harvard Neurodiscovery Center Predoctoral Fellowship
2001	Fulbright Postgraduate Award
2000	University of Sydney "Honors Class I" awarded for M.B.B.S. degrees
1998	Australian Medical Association JG Hunter Research Scholarship
1996	University of Sydney School of Mathematics Scholarship
1995	University of Sydney Renwick Prize for Greatest Proficiency in Neuroscience
1995	University of Sydney JT Wilson Prize for Neuroanatomy
1993	Australian Students Prize for Excellence
1993	Premier's Medal for TER 100 (ranked 3rd/61000 examinees)

C. Contribution to Science

1. A yeast-to-human neuron platform for biological and drug discovery in neurodegeneration

As a postdoctoral Fellow, I entered the iPSc modeling field at a nascent stage, shortly after the initial fundamental papers on somatic cell reprogramming were published. I **co-developed a platform that exploited the central role of protein-misfolding in neurodegeneration to identify and reverse early, innate pathologic phenotypes in Parkinson patient-derived neurons**. There were two components to this project's success: first, an upfront investment in time and effort to identify and recruit to our study a rare patient with a point mutation at the alpha-synuclein locus. This enabled us to generate isogenic mutation-corrected pairs of iPSc lines (in collaboration with Dr. Frank Soldner in the laboratory of Dr. Rudolf Jaenisch). Second, we developed a yeast-to-neuron platform through which information from unbiased genetic and small-molecule screens against proteotoxicities in simple Baker's yeast cells could be employed to pinpoint and reverse neuronal pathologies within neurons. We thus established that core mechanisms of neurodegenerative proteinopathy are conserved across a billion years of evolution. Moreover, the platform was capable of harnessing yeast genetics to identify the targets of effective small molecules, circumventing a major bottleneck in utilizing phenotypic screens for drug discovery. The platform identified Nedd4 and stearoyl-co-A desaturase (SCD) as novel druggable targets for Parkinson's disease, with SCD inhibitors now entering clinical trial. The platform also provided early validation for beta-2 adrenergic agonists as potential therapeutic compounds for Parkinson's disease.

a. Chung CY*, **Khurana V*,** Auluck PK, Tardiff DF, Mazzulli JR, Soldner F, Baru V, Lou Y, Freyzon Y, Cho S, Mungenast A, Muffat J, Mitalipova M, Pluth MD, Jui NT, Schüle B, Lippard SJ, Tsai LH, Krainc D, Buchwald, SL, Jaenisch R, Lindquist S. Identification and rescue of α-synuclein toxicity in Parkinson patient-derived neurons. ***Science*** 2013 342 (6161): 983-87. PMCID: PMC4022187. *Co-first authors.
b. Tardiff DF, Jui NT, **Khurana V**, Tambe M, Tucci ML, Chung CY, Lancaster AK, Caldwell KA, Caldwell GA, Rochet JC, Buchwald ST, Lindquist S. Yeast reveal a "druggable" Rsp5/Nedd4 network that ameliorates α-synuclein toxicity in neurons. ***Science***. 2013 342 (6161): 979-83. PMCID: PMC3993916.
c. Mittal S, Bjørnevik K, Im DS, Flierl A, Dong X, Locascio JJ, Abo KM, Long E, Jin M, Xu B, Xiang YK, Rochet JC, Engeland A, Rizzu P, Heutink P, Bartels T, Selkoe DJ, Caldarone BJ, Glicksman MA, **Khurana V**, Schüle B,

Park DS, Riise T, Scherzer CR. β2-Adrenoreceptor is a regulator of α-synuclein gene driving risk of Parkinson's disease. ***Science*** 2017 357(6354):891-898.

d. Vincent BM, Tardiff DF*, Piotrowski JS, Aron R, Lucas MC, Chung CY, Bacherman H, Chen Y, Pires M, Subramaniam R, Doshi D, Sadlish H, Raja WK, Solís EJ, **Khurana V**, Le Bourdonnec B, Scannevin RH, and Rhodes KJ. Stearoyl-CoA Desaturase as a novel therapeutic target for synucleinopathies. ***Cell Reports*** 2018 Dec 4;25(10):2742-2754

2. Genetic and spatial dissection of protein-misfolding pathology in living cells uncovers direct connections of α-synuclein to endocytic trafficking and mRNA metabolism

We established the first "maps" of proteotoxicities, identifying at proteome scale genetic and physical interactions of aggregating alpha-synuclein protein. First, we utilized systematic loss- and gain-of function genome-wide screens, combined with a novel computational methodology called TransposeNet, to provide a genome-scale view of the perturbed cellular physiology in neurodegeneration. TransposeNet, created in collaboration with Dr. Jian Peng now at the University of Illinois, recognizes the limitations in creating any molecular network from human proteins because of the relative sparsity of the human interactome. The tool enables mapping of molecular interactions across species to augment the human interactome. Homology mapping is achieved on the basis of sequence, predicted structure and network topology (protein-protein interaction information). TransposeNet synucleinopathy maps revealed specific molecular mechanisms through which diverse neurodegenerative disease genes connect to alpha-synuclein toxicity. Neurons derived from patients with three distinct forms of parkinsonism confirmed predictions of the molecular network. This work provides a method for stratifying patients according to genetic lesion and molecular mechanism, a critical need for neurodegenerative drug development. Second, in collaboration with Dr. Chee Yeun Chung and the laboratory of Dr. Alice Ting, I optimized a peroxidase-based method for *in situ* proteome mapping. This enabled us to map the local proteome of alpha-synuclein in living neurons at <10nm resolution and uncover a close connection between the spatial location of alpha-synuclein within a neuron and mechanisms through which it causes toxicity. Proteins most directly connected to α-syn were involved in endocytic protein trafficking and mRNA metabolism. The latter finding was unexpected and was further investigated. We validated numerous genetic and physical interactions between mRNA binding proteins and α-syn and identified a significant defect in mRNA translation in Parkinson patient neurons prior to ER stress. In a subsequent paper, we established a direct connection between α-syn and the decapping module of P-bodies, directly connecting α-syn to gene regulation.

a. **Khurana V***^{o}, Peng J*, Chung CY*, Auluck PK, Fanning S, Tardiff DF, Bartels T, Koeva M, Benyamini H, Lou Y, Nutter-Upham A, Tuncbag N, Baru V, Freyzon Y, Costanzo M, San-Luis B, Schöndorf DC, Barrasa MI, Caraveo G, Ehsani S, Sanjana N, Zhong Q, Gasser T, Vidal M, Deleidi M, Boone C, Berger B^{o}, Fraenkel E^{o}, Lindquist S. Genome-scale molecular networks link diverse neurodegenerative disease genes to alpha-synuclein through specific molecular pathways. ***Cell Systems*** 2017 4:157–170.e14. *Co-first and ^{o}co-corresponding authors. PMCID: PMC5388136

b. Chung, CY*^{o}, **Khurana, V***^{o}, Loh, K. H., Yi, S., Sahni, N., Auluck, P. K., Baru, V., Udeshi, N.D., Freyzon, Y., Carr, S.A., Hill, D.E., Vidal, M., Ting, A.Y, Lindquist. *In situ* proteome approaches connect alpha-synuclein directly to endocytic trafficking and mRNA biology in neurons. ***Cell Systems*** 2017 4**:**242–250.e4.*^{o}Co-first and co-corresponding authors. PMCID:PMC5578869

c. Hallacli E, Kayatekin C, Nazeen S , Wang X, Sheinkopf Z, Sathyakumar S, Sarkar S, Jiang X, Dong X, Di Maio R, Wang W, **Keeney MT**, Daniel Felsky, Sandoe J, Vahdatshoar A, Mani DR, Udeshi ND, Carr SA, de Jager P, Myers CL, Greenmyre TJ, Lindquist S, Bartel DP, Sunyaev S, Feany MB, Chung CY and **Khurana V***. The Parkinson's disease protein alpha-synuclein is a modulator of Processing-bodies and mRNA stability. ***Cell***. 2022 Jun 9;185(12):2035-2056.e33

3. Mechanisms of variable penetrance in alpha-synucleinopathy

Our proteotoxicity "maps" provide a framework for understanding gene-gene interactions that are involved in variable penetrance, and also understanding which key genetic "nodes" might interact with environmental toxicants to trigger synucleinopathy. Our gene-environment interaction work, in which toxicant data from real-world exposures is integrated into an *in vitro* iPSC DA neuron exposure paradigm has been supported by two Department of Defense grants that are collaborative with Dr Beate Ritz (UCLA) and Dr Lee Rubin (Harvard University). The first paper from this work has now been published. Additional work in this area is relatively new with papers now in preparation. We have: i) performed targeted exome sequencing off ~500 genes from our proteotoxicity networks in approximately 500 synucleinopathy patients; ii) sequenced the genomes, developed iPSC models and performed extensive analysis of the microbiome of a well-characterized multigeneration kindred harboring an alpha-synuclein (E46>K) mutation that exhibits striking variable penetrance; iii) developed a clinical paradigm for registering and longitudinally tracking our patients with

atypical parkinsonian disorders and multiple system atrophy (MSA); iv) established a syucleinopathy brain bank with approximately 50 brains, around 20 matched to iPSC lines. Our gene-gene interaction work feeds into large multi-center collaborations, including within the context of the Aligning Science Across Parkinson's (ASAP) consortium and multiple system atrophy (MSA) collaborative core initiative. Finally, to establish the next generation of human CNS models to screen, we developed a rapid, scalable tractable system for modeling advanced alpha-synuclein aggregation pathologies rapidly in the dish, a model we will use extensively in this grant proposal. The model achieves brain-like levels of expression of alpha-synuclein in CNS cell types. We have shown in detail that the pathologies formed in this model closely resemble pathologies in the human brain. In collaboration with Dr David Walt's lab (HMS/BWH/Wyss Inst), we are beginning to "digitize" a seed amplification assay (SAA) to better quantitate pathologies in these models.

a. Ndayisaba A, Pitaro A, Willett A...**Khurana, V* (50 authors).** Clinical trial-ready patient cohorts for multiple system atrophy: coupling biospecimen and iPSC banking to longitudinal deep-phenotyping. ***Cerebellum*** 2022. doi: 10.1007/s12311-022-01501-5. [x]corresponding author.

b. Paul KC*, **Krolewski RC*,** Lucumi Moreno E, Blank J, Holton K, Ahfeldt T, Furlong M, Yu Y, Cockburn M, Thompson LK, Bronstein J, Rubin L[x], Khurana V[x], and Ritz B[x]. Coupling comprehensive pesticide-wide association study to iPSC dopaminergic screening identifies and classifies Parkinson-relevant pesticides. ***Nature Communications*** 2023. Accepted. *co-first authors; [x]co-corresponding authors.

c. Lam I, Ndayisaba A, Lewis AJ, Fu YH, Zaccagnini L, Sandoe J, Sanz R, Vahdatshoar A, Martin TD, Nader M, Ichihashi T, Tripathi A, Ramalingam N, Oettgen C, Bartels T, Schäbinger M, Jiang X, Verma A, Yu X, Hyles K, Park C, Theunissen TW, Wang H, Jaenisch R, Stevens B, Stefanova N, Wenning G, Luk KC, Pernaute RS, Gómez-Esteban JC, Felsky D, Kiyota Y, Sahni N, Yi S, Chung CY, Stahlberg H, Abizanda IF, Schöneberg J, Elledge SJ, Dettmer U, Halliday GM, Bartels T, and **Khurana V**. Rapid iPSC inclusionopathy models shed light on formation, consequence and molecular subtype of proteinaceous a-synuclein inclusions. ***Neuron,*** https://doi.org/10.1016/j.neuron.2024.06.002 (July 29 2024).

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